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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/062,257	ITOH, KYOGO	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/10/06, 5/24/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-123* is/are pending in the application.

4a) Of the above claim(s) *5,6,9-43,46-116 and 118-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,44,45 and 117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/03,3/20/02,4/12/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants are required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 37 at Table 5 [SEQ ID NO: 10], page 14 at lines 11-14, page 13 at line 20 and page 36 at lines 16 and 20. It is noted by the Examiner with regard to the sequence DYLRSV that appears on pages 13 and 36 at the cited locations, said sequence is a subsequence of SEQ ID NO: 2, *i.e.,* amino acid residues 1-6, and said sequence may be identified thus).

2. Applicant's amendment filed 2/10/06 and Applicant's response filed 5/24/06 are acknowledged and have been entered.

3. Applicant's election with traverse of Group I drawn to the peptide having an amino acid sequence of SEQ ID NO: 1, and inducer of CTL thereof, vaccine thereof, and pharmaceutical composition thereof (claims 1, 3, 7 and 44) in Applicant's response filed 5/24/06 is acknowledged.

The basis for Applicant's traversal is of record on pages 4-7 of the said response, briefly that there appears to be no serious burden to search the entire scope of the claims, the number of restricted groups is indicative of error in the restriction requirement, unity exists within all claims, the ISA found a single inventive concept by examining all the claims, Applicant believes that SEQ ID NO: 1-3 should be examined together as they are peptides from Lck protein that have the HLA-A24 binding motif and induce an HLA-A24-restricted response, and SEQ ID NO: 1 and 2 have a high percent amino acid similarity.

It is the Examiner's position that: (1) the restriction requirement was to GROUPS, not species, (2) the instant application is not a 371 filing, but a CIP of PCT/JP00/05220, (3) the number of groups is indicative of the number of inventions recited in the claims, (4) restriction to one invention was required under 35 USC 121, lack of unity under 1.475 was not, (5) the peptides of Groups I-III are from Lck protein and bind to HLA-A24, the peptides of Groups IV-IX are from different proteins (*i.e.,* Src511-519, yes508-516, Fyn512-520, Lyn489-497, Hck503-511 and Vlk482-490), and the peptides of Groups XI-XVI bind to a different HLA molecule, HLA-A2. All the peptides have different primary sequences, necessitating separate searches in protein databases, as well as separate searches in patent and non-patent literature with regard to their proteins of origin and/or HLA restriction. Regarding undue burden, the M.P.E.P. 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search, (6) The inventions are distinct for reasons elaborated in paragraphs 16-28 of the previous Office Action. Thus, the two criteria for a proper requirement for restriction between

patentably distinct inventions, *i.e.,* distinct as claimed and serious burden on the Examiner by the examination of additional groups, have been established by the previous Office Action.

However, the Examiner will rejoin Groups I, II and III (SEQ ID NO: 1-3) and examine them together.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 5, 6, 9-43, 46-116 and 118-123 (Groups XVII-CLXXXV) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-4, 7, 8, 44, 45 and 117 are presently being examined as they read on Groups I, II and III (SEQ ID NO: 1-3).

4. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. See MPEP 608.01(b).

The Abstract discloses "A tumor antigen peptide...functions by providing a polynucleotide encoding the peptide..." The Examiner notes that a peptide cannot function by providing a polynucleotide. The Examiner would like clarification if the said disclosure is an incorrect translation of the abstract in the parent PCT/JP00/05220 which is incorporated by reference. Applicant is cautioned that if said disclosure is not an incorrect translation, removing said disclosure might constitute new matter.

5. The Examiner notes that there are two sets of the specification filed on the same date, *i.e.,* 2/1/02, wherein one of the copies has two sets of different page numbers on each page.

6. following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

a. Claims 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the

inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed inducer of CTL recited in instant claims 3 and 4, wherein the said inducer comprises at least the peptide of claim 1 or claim 2, and wherein the other components of the "inducer" are not disclosed.

The instant claims encompass "inducers" of CTL that comprise the peptide of claim 1 or claim 2 and numerous other undisclosed components.

The specification discloses that SEQ ID NO: 11, 12 and 16 can be used as inducers for inducing CTL (page 16 at lines 5-25 and page 17 at lines 1-8).

The specification does not disclose the definition of "inducer."

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any peptide or non-peptide of an "inducer." Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

b. Claims 7, 8, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed pharmaceutical composition recited in instant claims 44 and 45, said pharmaceutical composition comprising an effective amount for cancer treatment of at least one peptide of claim 1 or claim 2, nor the cancer vaccine recited in instant claims 7 and 8, said cancer vaccine comprising at least the peptide of claim 1 or claim 2.

The instant claims encompass a pharmaceutical composition comprising an amount of at least one of the peptides of claim 1 or claim 2 effective for cancer treatment, or a cancer vaccine comprising the peptide of claim 1 or claim 2.

The specification discloses that SEQ ID NO: 1-3 are subsequence peptides of the lck protein that is over-expressed on adenocarcinoma cells or epithelial cancer cells in colon or small cell lung cancers bound to HLA-A2402, exhibited a CTL-activating ability of PBMC from a cancer patient (or PMBC from normal individuals when presented by HLA-A2402 on professional APC dendritic cells), as well as enhancing the production of IFN-γ by CTLs. The specification discloses that CTL induced by the said SEQ ID NO could recognize a tumor cell line (paragraph spanning pages 4-5, page 7 at lines 21-25, paragraph spanning pages 10-11, page 11 at lines 19-24, pages 12-13, Table 1 on page 28, Examples 4-6).

The specification further discloses that the amino acid sequence DYLRSV, common to both SEQ ID NO: 1 and 2, has a relevance to tumor rejection. The specification discloses searching for homologous sequences in other proteins, and testing subseqence 9-mer peptides from some of the tyrosine kinase proteins for binding to HLA-A2402 and for stimulating CTL (especially Examples 6-7). Larger 13-mer subsequences containing these peptides conform to the formula that is SEQ ID NO: 10 (Example 6).

There are no working examples of any *in vivo* method of treatment with the said peptide, and in addition, the specification does not provide adequate written description for "treating." The specification does not does not provide description that administration of the peptide produces such a CTL response that "treats."

The specification does not disclose working examples of any peptide recited in claim 1 or claim 2 used for treatment or for prophylaxis as a vaccine.

Evidentiary reference Marchand *et al* (Int. J. Cancer 20: 219-230, 1999) teach "Considerable further progress is needed... before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy." (second to last sentence of article).

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endopoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference the Merck Manual teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein.

c. Claims 1-4, 7, 8, 44, 45 and 117 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed peptide *having* "an" amino acid sequence of the SEQ ID NO recited in instant claim 1/inducer, vaccine or pharmaceutical composition thereof, nor of the claimed peptide *having* "an" amino acid sequence of SEQ ID NO: 10 recited in claim 2/kit comprising said peptide/inducer, vaccine or pharmaceutical composition thereof.

The instant claims encompass: (1) a peptide *having* (*i.e.,* comprising) a subsequence of one of the SEQ ID NO recited in instant claim 1, said subsequence does not bind to HLA-A2402 and elicit an immune response and that in addition may comprise additional undisclosed flanking regions, (2) a peptide *having* a peptide (*i.e.,* comprising) a subsequence of SEQ ID NO: 10 that is not one of SEQ ID NO: 1, 2, 4-9, but is rather a subsequence of SEQ ID NO: 10 that does not bind to HLA-A2402 and elicit an immune response and that in addition may comprise additional undisclosed flanking regions, or (3) having the amino acid sequence of one of the SEQ ID NO recited in instant claims 1 or 2 with undisclosed flanking sequences.

The specification discloses that SEQ ID NO: 1-3 are subsequence peptides of the lck protein that is over-expressed on adenocarcinoma cells or epithelial cancer cells in colon or small cell lung cancers bound to HLA-A2402, exhibited a CTL-activating ability of PBMC from a cancer patient (or PMBC from normal individuals when presented by HLA-A2402 on professional APC dendritic cells), as well as enhancing the production of IFN-γ by CTLs. The specification discloses that CTL induced by the said SEQ ID NO could recognize a tumor cell line (paragraph spanning pages 4-5, page 7 at lines 21-25, paragraph spanning pages 10-11, page 11 at lines 19-24, pages 12-13, Table 1 on page 28, Examples 4-6).

The specification further discloses that the amino acid sequence DYLRSV, common to both SEQ ID NO: 1 and 2, has a relevance to tumor rejection. The specification discloses searching for homologous sequences in other proteins, and testing subseqence 9-mer peptides from some of the tyrosine kinase proteins for binding to HLA-A2402 and for stimulating CTL (especially Examples 6-7). Larger 13-mer subsequences containing these peptides conform to the formula that is SEQ ID NO: 10 (Example 6).

There are no working examples of any smaller subsequences of SEQ ID NO: 1-3 that are shorter than 9 or 10 amino acid residues in length, or subsequences of SEQ ID NO: 10 that do not contain one of SEQ ID NO: 1, 2, 4-9, and/or that contain additional undisclosed flanking amino acid sequence.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein.

7. Claims 1-4, 7, 8, 44, 45 and 117 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. The specification does not disclose how to make and/or use the instant invention, the claimed inducer of CTL recited in instant claims 3 and 4, wherein the said inducer comprises at least the peptide of claim 1 or claim 2, and wherein the other components of the "inducer" are not disclosed.

The specification does not disclose how to make and/or use the instant invention, "inducers" of CTL that comprise the peptide of claim 1 or claim 2 and numerous other undisclosed components. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited inducer can be made and/or used.

The specification discloses that SEQ ID NO: 11, 12 and 16 can be used as inducers for inducing CTL (page 16 at lines 5-25 and page 17 at lines 1-8).

The specification does not disclose the definition of "inducer."

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine" (last paragraph at column 2 on page 505).

Evidentiary reference Paul (Fundamental Immunology, 2nd Edition, 1989, page 1006, column 1 at the second full paragraph) teaches "It seems that both T and B memory cells are more readily stimulated to become effector cells compared to naïve cells..."

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

b. The specification does not disclose how to make and/or use the instant invention, the claimed pharmaceutical composition recited in instant claims 44 and 45, said pharmaceutical composition comprising an effective amount for cancer treatment of at least one peptide of claim 1 or claim 2, nor the cancer vaccine recited in instant claims 7 and 8, said cancer vaccine comprising at least the peptide of claim 1 or claim 2. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited inducer can be made and/or used.

The instant claims encompass a pharmaceutical composition comprising an amount of at least one of the peptides of claim 1 or claim 2 effective for cancer treatment, or a cancer vaccine comprising the peptide of claim 1 or claim 2.

The specification discloses that SEQ ID NO: 1-3 are subsequence peptides of the lck protein that is over-expressed on adenocarcinoma cells or epithelial cancer cells in colon or small cell lung cancers bound to HLA-A2402, exhibited a CTL-activating ability of PBMC from a cancer patient (or PMBC from normal individuals when presented by HLA-A2402 on professional APC dendritic cells), as well as enhancing the production of IFN-γ by CTLs. The specification discloses that CTL induced by the said SEQ ID NO could recognize a tumor cell line (paragraph spanning pages 4-5, page 7 at lines 21-25, paragraph spanning pages 10-11, page 11 at lines 19-24, pages 12-13, Table 1 on page 28, Examples 4-6).

The specification further discloses that the amino acid sequence DYLRSV, common to both SEQ ID NO: 1 and 2, has a relevance to tumor rejection. The specification discloses searching for homologous sequences in other proteins, and testing subseqence 9-mer peptides from some of the tyrosine kinase proteins for binding to HLA-A2402 and for stimulating CTL (especially Examples 6-7). Larger 13-mer subsequences containing these peptides conform to the formula that is SEQ ID NO: 10 (Example 6).

There are no working examples of any *in vivo* method of treatment with the claimed peptides, and in addition, the specification does not provide a definition for effective treatment of cancer. The specification does not does not provide disclosure that administration of the peptide *in vivo* produces a CTL response that "treats" cancer.

The specification does not disclose working examples of any peptide recited in claim 1 or claim 2 used for treatment or for prophylaxis as a vaccine.

Evidentiary reference Marchand *et al* (Int. J. Cancer 20: 219-230, 1999) teach "Considerable further progress is needed... before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy." (second to last sentence of article).

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

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Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endopoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference the Merck Manual teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

c. The specification does not disclose how to make and/or use the instant invention, the claimed peptide *having* "an" amino acid sequence of the SEQ ID NO recited in instant claim 1/inducer, vaccine or pharmaceutical composition thereof, nor of the claimed peptide *having* "an" amino acid sequence of SEQ ID NO: 10 recited in claim 2/kit comprising said peptide/inducer, vaccine, or pharmaceutical composition thereof. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited peptide can be made and/or used.

The instant claims encompass: (1) a peptide *having* (*i.e.,* comprising) a subsequence of one of the SEQ ID NO recited in instant claim 1, said subsequence does not bind to HLA-A2402 and elicit an immune response, and that in addition may comprise additional undisclosed flanking regions, (2) a peptide *having* a peptide (*i.e.,* comprising) a subsequence of SEQ ID NO: 10 that is not one of SEQ ID NO: 1, 2, 4-9, but is rather a subsequence of SEQ ID NO: 10 that does not bind to HLA-A2402 and elicit an immune response and that in addition may comprise additional undisclosed flanking regions, or (3) having the amino acid sequence of one of the SEQ ID NO recited in instant claims 1 or 2 with undisclosed flanking sequences, or (4) the peptide consisting of SEQ ID NO: 10.

The specification discloses that SEQ ID NO: 1-3 are subsequence peptides of the Lck protein that is over-expressed on adenocarcinoma cells or epithelial cancer cells in colon or small cell lung cancers bound to HLA-A2402, exhibited a CTL-activating ability of PBMC from a cancer patient (or PMBC from normal individuals when presented by HLA-A2402 on professional APC dendritic cells), as well as enhancing the production of IFN-γ by CTLs. The specification discloses that CTL induced by the said SEQ ID NO could recognize a tumor cell line (paragraph spanning pages 4-5, page 7 at lines 21-25, paragraph spanning pages 10-11, page 11 at lines 19-24, pages 12-13, Table 1 on page 28, Examples 4-6).

The specification further discloses that the amino acid sequence DYLRSV, common to both SEQ ID NO: 1 and 2, has a relevance to tumor rejection. The specification discloses searching for homologous sequences in other proteins, and testing subseqence 9-mer peptides from some of the tyrosine kinase proteins for binding to HLA-A2402 and for stimulating CTL (especially Examples 6-7). Larger 13-mer subsequences containing these peptides conform to the formula that is SEQ ID NO: 10 (Example 6).

There are no working examples of any smaller subsequences of SEQ ID NO: 1-3 that are shorter than 9 or 10 amino acid residues in length, or that do not contain one of SEQ ID NO: 1, 2, 4-9, and/or that contain additional undisclosed flanking amino acid sequence. There are no working examples of any peptide consisting of the sequence of SEQ ID NO: 10 that bind to an HLA class I molecule and elicit a CTL response, though smaller 9 or 10-mer subsequences of the optimal length to bind to an HLA class I molecule are disclosed in the instant specification to stimulate CTL *in vitro*.

There is no guarantee that the claimed peptide would bind to HLA and would be recognized by CTL, *i.e.,* be a T cell epitope. The specification provides no evidence that the peptide consisting of some subsequence of one of SEQ ID NO: 1-3 or 10: (1) would bind to an MHC molecule either by itself or when present in a longer peptide of unknown length and flanked by amino acid sequences not present in the antigenic protein of origin, (2) or would be recognized by CTL. The specification provides no evidence that the peptide consisting of SEQ ID NO: 10 (13-mer peptide) would bind to an HLA class I molecule or would be recognized by CTL.

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr *et al*, Shastri *et al*, Bergmann *et al*, Wang *et al*, Perkins *et al*, Theoboald *et al* and Gileadi *et al*) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins *et al*) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang *et al*). An undue amount of experimentation would be involved in determining longer peptides from the many possibilities that would be capable of binding to HLA and being recognized by CTL.

The art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends," but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-4, 7, 8, 44, 45 and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 2 are indefinite in the recitation of "having an" amino acid sequence of SEQ ID NO because it is not clear what is meant, *i.e.,* what the metes and bounds of the claims are.

b. Claims 3 and 4 are indefinite in the recitation of "An inducer of cytotoxic T lymphocytes" because it is not clear what is meant. The instant specification does not disclose the definition of "An inducer of cytotoxic T lymphocytes."

c. Claims 44 and 45 are indefinite in the recitation of "of at last one selected from the peptides of claim" because it is not clear what is meant.

d. Claim 117 is indefinite in the recitation of "enhances the recognition property by HLA-A2402-restricted cytotoxic T lymphocytes" because it is not clear what is meant.

e. Claim 117 is indefinite in the recitation of ""at least one or more peptide(s) according to claim 2" because it is not clear what is meant, *i.e,* claim 2 recites "A peptide..."

10. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 7, 8, 44, 45 and 117 are deemed to be the filing date of the instant application, *i.e.,* 2/1/02, since translations of the parent applications have not been provided by Applicant.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Voronova *et al* (Nature, 319, 682-685, 1986, IDS reference).

Voronova *et al* teach a polypeptide comprising or *having* the sequence of SEQ ID NO: 1 and 3 (Figure 1 on page 683).

13. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Harashima *et al* (Eur. J. Immunol. 31: 323-332, 2001, IDS reference, date of public availability 1/22/01.)

Harashima *et al* teach peptides consisting of the sequence of SEQ ID NO: 1, 2 and 3 of the instant claims that as HLA-A24 class I restricted antigenic epitopes, induce CTL production from PBMC of epithelial cancer patients and healthy donors (see entire reference, especially abstract, section 2.3, discussion). Harashima *et al* teach that the peptides corresponding to SEQ ID NO: 1 and 2 are the major epitopes recognized by CTL. Harashima *et al* further teach that they identified two Lck-derived peptides that induce HLA-A2 restricted CTL in HLA-$A2^+$ metastatic cancer patients (last paragraph). SEQ ID NO: 1 and 2 are peptides that are a subsequence of SEQ ID NO: 10 of the instant claim 2, *i.e.,* are peptides "having an amino acid sequence of SEQ ID NO: 10."

14. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/22255 A1.

WO 97/22255 A1 teaches a peptide comprising SEQ ID NO: 3 of the instant claims, SEQ ID NO: 3 being a subsequence of SEQ ID NO: 10 of instant claim 2, or a "peptide having an amino acid sequence of SEQ ID NO: 10" (especially page 11 at lines 25-26, Figure 5, page 18 at lines 30-33 and page 46 at lines 30-35).

Claims 3 and 4 are included in this rejection because while the art reference is silent as to whether the composition is an inducer of CTLs, the claimed peptide appears to be the same as that of the prior art reference, absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the peptide of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252,195 USPQ 430 (CCPA 1977).

15. Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,635,623 B1.

US 6,635,623 B1 discloses a peptide comprising SEQ ID NO: 1 and 2 of the instant claims (SEQ ID NO: 74 of the art reference).

Claims 3 and 4 are included in this rejection because while the art reference is silent as to whether the composition is an inducer of CTLs, the claimed peptide appears to be the same as that of the prior art reference, absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the peptide of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252,195 USPQ 430 (CCPA 1977).

16. Claims 1-4, 7, 8, 44 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,432,076.

US 5,432,076 discloses a peptide comprising SEQ ID NO: 1 and 2 of the instant claims (the sequence appearing at column 5, lines 23-27 of the art reference). US 5,432,076 discloses that the said peptide was used to raise an antiserum in rabbits, *i.e,* the composition is a pharmaceutical composition.

Claims 3 and 4 are included in this rejection because while the art reference is silent as to whether the composition is an inducer of CTLs, the claimed pharmaceutical composition appears to be the same as that of the prior art reference, absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the

pharmaceutical composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252,195 USPQ 430 (CCPA 1977).

Claims 7 and 8 are included in this rejection because the recitation of the limitation "vaccine" does not impart a structural difference on a known composition. With regard to the recitation of "cancer vaccine" in instant claims 7 and 8, the recitation of "cancer vaccine" also does not impart a structural difference on a known composition. In addition, although the art reference does not teach that the pharmaceutical composition has the intended use as a cancer vaccine, the claimed pharmaceutical composition appears to be the same as that of the prior art reference, absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the pharmaceutical composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252,195 USPQ 430 (CCPA 1977).

With regard to the recitation of "for cancer treatment" in instant claims 44 and 45, the recitation of intended use does not carry patentable weight per se and the claims read on the active or essential ingredients of the composition.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-4, 7, 8, 44, 45 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harashima *et al* (Eur. J. Immunol. 31: 323-332, 2001, IDS reference, date of public availability 1/22/01) in view of US 5,734,023 and De Bruijin *et al* (Eur. J. Immunol. 1991, 21: 2963-2790).

Harashima *et al* teach peptides consisting of the sequence of SEQ ID NO: 1, 2 and 3 of the instant claims that as HLA-A24 class I restricted antigenic eptiopes, induce CTL production from PBMC of epithelial cancer patients and healthy donors (see entire reference, especially abstract, section 2.3, discussion). Harashima *et al* teach that the peptides corresponding to SEQ ID NO: 1 and 2 are the major epitopes recognized by CTL. SEQ ID NO: 1 and 2 are peptides that are a subsequence of SEQ ID NO: 10 of the instant claim 2, *i.e.,* are peptides "having an amino acid sequence of SEQ ID NO: 10." Harashima *et al* further teach that they identified two Lck-derived peptides that induce HLA-A2 restricted CTL in HLA-$A2^+$ metastatic cancer patients (last paragraph). Harashima *et al* are silent as to the diluent or excipient HLA-A24 restricted peptides are formulated in, so do not teach a pharmaceutical composition comprising SEQ ID NO: 1,

2 or 3. Harashima *et al* teach that Lck peptides could be useful in developing a specific immunotherapy for cancer patients with distant metastases (abstract).

Harashima *et al* however, do teach a pharmaceutical compositions comprising HLA-A2 restricted lck peptides that were injected into metastatic cancer patients.

US 5,734,023 discloses that PBS is a pharmaceutical carrier for proteins and peptides, and further teaches formulating immunogenic peptides in kits for therapeutic use (especially column 27 at lines 34-62 and column 28 at lines 62-65).

De Bruijin *et al* teaches formulating epitope peptides in PBS for *in vitro* T cell assay (especially section 2.2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the HLA-A24 restricted CTL epitopes taught by Harashima *et al* in PBS as disclosed by US 5,734,023 and De Bruijin *et al*. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the peptides taught by Harashima *et al* in a kit as disclosed by US 5,734,023 for other immunogenic peptides.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to formulate a vaccine for HLA-A24 positive metatstatic cancer patients, such as taught for the HLA-A2 positive patients with the HLA-A2 restricted CTL epitopes, using PBS that is a pharmaceutical carrier as disclosed by US 5,734,023 and as taught by De Bruijin *et al* as useful for formulating epitope peptides for *in vitro* T cell assay. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Harashima *et al* teach that the CTL epitope peptides can elicit CTL and that the peptides corresponding to SEQ ID NO: 1 and 2 of the instant claims are major immunogenic epitopes recognized by CTL. One of ordinary skill in the art at the time the invention was made would have been motivated to include the peptides taught by Harashima *et al* in a kit as disclosed by US 5,734,023 because US 5,734,023 discloses the usefulness of including other immunogenic peptides in a kit.

Claims 7 and 8 are included in this rejection because the recitation of the limitation "vaccine" does not impart a structural difference on a known composition. With regard to the recitation of "cancer vaccine" in instant claims 7 and 8, the recitation of "cancer vaccine" also does not impart a structural difference on a known composition.

With regard to the recitation of the intended use in instant claim 117, the recitation of intended use does not carry patentable weight per se and the claim reads on the active or essential ingredients of the kit.

19. Claims 1-4, 7, 8, 44, 45 and 117are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,432,076 in view of US 5,734,023.

US 5,432,076 discloses a peptide comprising SEQ ID NO: 1 and 2 of the instant claims (the sequence appearing at column 5, lines 23-27 of the art reference). US 5,432,076 discloses that the said peptide was used to raise an antiserum in rabbits, *i.e,* the composition is a pharmaceutical composition.

US 5,432,076 does not disclose the peptide(s) formulated in a kit.

US 5,734,023 discloses that PBS is a pharmaceutical carrier for proteins and peptides and further teaches formulating immunogenic peptides in kits for therapeutic use (especially column 27 at lines 34-62 and column 28 at lines 62-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptides disclosed by US 5,432,076 in a kit as disclosed by US 5,734,023.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because both US 5,432,076 and US 5,734,023 disclose immunogenic peptides, and US 5,734,023 discloses formulating the immunogenic peptides in kits for therapeutic use.

Claims 3 and 4 are included in this rejection because while the art reference is silent as to whether the composition is an inducer of CTLs, the claimed pharmaceutical composition appears to be similar to that of the prior art reference, absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the pharmaceutical composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252,195 USPQ 430 (CCPA 1977).

Claims 7 and 8 are included in this rejection because the recitation of the limitation "vaccine" does not impart a structural difference on a known composition. With regard to the recitation of "cancer vaccine" in instant claims 7 and 8, the recitation of "cancer vaccine" also does not impart a structural difference on a known composition. In addition, although the art reference does not teach that the pharmaceutical composition has the intended use as a cancer vaccine, the claimed pharmaceutical composition appears to be similar to that of the prior art reference, absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the pharmaceutical composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252,195 USPQ 430 (CCPA 1977).

With regard to the recitation of "for cancer treatment" in instant claims 44 and 45, the recitation of intended use does not carry patentable weight per se and the claims read on the active or essential ingredients of the composition.

With regard to the recitation of the intended use in instant claim 117, the recitation of intended use does not carry patentable weight per se and the claim reads on the active or essential ingredients of the kit.

20. No claim is allowed.

21. The references crossed out in Applicant's Form 1449 filed 7/11/03 are duplicate citations of references in Applicant's Form 1449 filed 3/20/02.

22. Claims 1 and 44 are objected to because of the following informalities:

a. Claim 1 is objected to for the recitation of "in the sequence listing." because the recited SEQ ID NO are present in the sequence listing.

b. Claim 44 is objected to for not having a period after the claim number "44".

Appropriate corrections are required.

23. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

24. The information disclosure statement filed 6/14/02 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Specifically, the Form 1449 filed 6/14/02 does not list any patent or non-patent or other information as enunciated in "(1)" of this paragraph.

25. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
July 28, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600